

## REMARKS

The present invention relates to isolated marrow stromal cells ("MSCs") for use in treatment of a central nervous system ("CNS") disease, disorder or condition in a patient. The invention includes methods directing the *in vivo* differentiation of isolated marrow stromal cells in the CNS of a human patient. Moreover, the stromal cells may be optionally cultured *in vitro* and/or may be genetically engineered to produce therapeutic compounds, and/or may be pre-differentiated prior to administration into the CNS.

Claims 1-18 are pending in the application following entry of the present Amendment. Claims 19 and 20 have been canceled previously in the Preliminary Amendment filed June 27, 2003, as being allowed in parent U.S. Application No. 09/028,395. Claims 1, 9, 11 and 16 have been amended herein to more particularly point out and distinctly claim the subject matter which Applicants regard as their invention.

The following constitutes a response to the Examiner's rejections stated in the Office Action dated August 16, 2002 (Paper No. 33) in parent U.S. Application No. 09/028,395.

Applicants respectfully submit, as more fully set forth below, that the present Second Preliminary Amendment serves to place claims 1-18 in condition for allowance.

### Rejection of Claims 1-18, under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 1-18 in the parent application under 35 U.S.C. § 112, first paragraph, because in the Examiner's opinion, cell and gene therapy using marrow stromal cells was not enabled by the disclosure in the specification given the unpredictability of the art at the time of filing. Applicants have previously addressed this rejection in Responses to prior Office Actions, which Responses were filed on May 28, 2002 (responding to Office Action mailed November 26, 2001; Paper No. 24), February 10, 2000 (responding to Office Action mailed October 4, 1999; Paper No. 6), November 20, 2000 (responding to Office Action mailed May 24, 2000; Paper No. 12), and by arguments presented by way of Preliminary Amendment and an accompanying Declaration of co-inventor, Darwin J. Prockop, pursuant to 37 C.F.R. 1.132 ("the Declaration"), filed on August 31, 2001. Applicants hereby incorporate by reference the arguments set forth in those Responses as if set forth in their entirety herein.

While Applicants cannot agree with the Examiner's stance regarding the enablement of the claims, in a good faith effort to expedite the prosecution of the present claims,

Applicants have amended the claims to delete reference to “treating” per se, and instead have amended the claims to recite “a method of directing differentiation of an isolated stromal cell to a neural cell” in a human. Applicants will file a continuation application to pursue the contested subject matter at a later date and therefore the present amendments to the claims should in no way be construed as surrendering any subject matter. The claims as amended are fully enabled by the specification as filed as set forth below. Further, the amendments do not add new matter as support for the amendments is found in the specification in Figures 5 and 6 and the description thereof.

As an initial matter and as previously set out for the Examiner, it is well-settled that an applicant need not have actually reduced the invention to practice prior to filing in order to satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph. MPEP §2164.02 (citing *Gould v. Quigg*, 882 F.2d 1074 (Fed. Cir. 1987)). Indeed, the invention need not contain a single example if the invention is otherwise disclosed in such a manner that one of skill in the art will be able to practice it without undue experimentation (*In re Borkowski*, 422 F.2d at 908), and “representative samples are not required by the statute and are not an end in themselves” (*In re Robbins*, 429 F.2d 452, 456-457, 166 USPQ 522, 555 (CCPA 1970)). Thus, 35 U.S.C § 112, first paragraph, enablement does not require any working examples.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. MPEP §2164.01 (citing *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976)). The fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. *Id.* Further, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled in the art and is already available to the public. MPEP §2164.05(a) (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)). Therefore, under current law, enablement does not require a working example and experimentation is allowed, so long as it is not undue.

Applicants respectfully submit that the as-filed specification is fully enabled for the method of directing differentiation of an isolated stromal cell into a neural cell in a human patient. The specification teaches neurotransplantation of an MSC in a mammal, and following neurotransplantation, the specification teaches that the transplanted cell is able to engraft, migrate, and survive in the striatum. For example, Figure 5 demonstrates that no significant

gliosis around the implantation was found following transplantation of the cell into the corpus striatum. Further, Figure 6 demonstrates that the donor cells were able to migrate following neurotransplantation, whereby the cells were found to migrate to multiple areas of the brain, including the contralateral cortex, rostrocaudal axis in the striatum and along the corpus callosum. Accordingly, Applicants respectfully submit that the amendments to claims 1, 9, 11 and 16 are supported by the as-filed specification and does not add new matter in any way.

In addition, Applicants further submit herewith the post-filing reference of Hofstetter et al. (2002, PNAS 99:2199-2204), wherein Dr. Darwin Prockop is a co-author, to demonstrate that the invention has been further reduced to practice by Applicants whereby the same methods as those included in the application were utilized to arrive at the results predicted in the as-filed application. This reference provides evidence that the disclosure of the as-filed specification enables the claimed invention. For example, Hofstetter et al. demonstrates that MSCs were able to survive and possess characteristics of neurons following transplantation into Rats.

Accordingly, Applicants respectfully submit that claims 1-18 are amply supported by the numerous working examples provided in the specification as filed, and as demonstrated by the post-filing reference of Hofstetter et al., wherein the results are arrived using the same methods as disclosed in the specification as filed.

Summary

Applicants respectfully submit that pending claims 1-18 following entry of the present Amendment are in condition for allowance. Allowance of claims 1-18 is respectfully requested at the earliest possible date.

Respectfully submitted,

**DARWIN J. PROCKOP ET AL.**

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(Date)

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Enclosure: Hofstetter et al. (2002, PNAS 99:2199-2204).